REMARKS

Claims 1, 3, 11, and 14, as herein amended, and claims 13 and 16 as filed, are pending. Claims 5-10, 13 and 17-22 have been withdrawn from consideration without prejudice or disclaimer in response to the restriction requirement, and claims 2, 4, 12 and 15 have been cancelled without prejudice. Applicant wishes to retain his rejoinder rights to all claims capable of rejoinder, and elect to defer making any required amendments until such time as the pending claims are acknowledged to be patentable.

All grounds of rejection to any cancelled claim are not addressed in this response, as Applicant's cancellation thereof has rendered these rejections moot.

The claims, as amended, fulfill the requirements of 35 U.S.C. §112.

All pending claims stand rejected under 35 U.S.C. §112, first paragraph for failing to satisfy the enablement requirement. The Action acknowledges that the claims are enabled for detecting her2/neu in blood plasma or serum in patients having certain cancers, it asserts that the claims as filed are not enabled throughout their full scope.

Without acquiescing to the asserted grounds of rejection, Applicant has amended his pending claims to recite that his invention is directed to detecting one or more species of RNA that is epidermal growth factor RNA, epidermal growth factor receptor RNA, her-2/neu RNA, c-myc RNA, or heterogeneous nuclear ribonucleoprotein A2/B1 RNA in human blood plasma or serum. Applicant's amendment thus addresses the issues raised in the justification for the rejection contained in the Action. Thus, the amendments to claim 1 overcome the rejection based on the confounding effect of the presence of heterogeneous nuclear ribonucleoprotein A2/B1 RNA in human blood plasma or serum from bronchial epithelial cells in chronic smokers, as the claim now recites detection of these species which is fully enabled by the claim. Moreover, Applicant respectfully contends that detection of multiple species by coordinate amplification techniques (i.e., specific amplification of different species contained in the same sample) is well-known in the art, by using specific primers that produce amplified fragments having a size characteristic for each amplified species. With regard to Claim 3, Applicant's amendments address the issue of enablement by limiting the claim to hybridization of her-2/neu RNA extracted from human blood plasma or serum using a probe specific thereto. Claim 3 is further amended to be directed to a human with breast cancer, thus excluding from the scope of

McDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 South Wacker Drive
Chicago, Illinois 60606
(312) 913-0001

the claim instances where Hodgkin's or non-Hodgkin's lymphoma patients fail to express her-2/neu. The amendments to claim 11 specify that detection of her-2/neu RNA be used to evaluate a human for a cancer-related treatment; Applicant respectfully contends that the presence of her-2/neu in some non-cancerous human cells is not relevant to the enablement question, since the claimed method is specific for evaluating patients known to have cancer, and does not require differentiating the cancer patient from a human without cancer. Claim 14 is amended to be directed to human breast cancer patients, thus excluding from the scope of the claim instances where Hodgkin's or non-Hodgkin's lymphoma patients fail to express her-2/neu.

Applicant thus respectfully contends that these amendments overcome the asserted ground of rejection, and request the Examiner to withdraw this ground of rejection.

Claims 1, 11-13 stand rejected under 35 U.S.C. §112, second paragraph as being indefinite. Applicant has amended these claims to overcome the asserted ground of rejection, and request the Examiner to withdraw these rejections.

The claims are not anticipated by the cited reference.

Claim 1 stands rejected as being anticipated under 35 U.S.C. 102(b) over the Balazs reference. The Action asserts that Balazs teaches detection of epidermal growth factor receptor RNA and c-myc by extracting total extracellular RNA from plasma or serum (page 11 of office action). Applicant respectfully contend that the teachings of the Balazs reference do not enable nor anticipate Applicant's claims, because they do not teach extraction of total extracellular RNA from plasma or serum.

In this regard, Applicant draws the Office's attention to the teaching of the Balazs reference that a nuclease inhibitor (specifically, an RNase inhibitor) be mixed with whole blood prior to separating plasma from the cellular fraction of the blood. Applicant respectfully contends that this teaching of the Balazs reference is important, in view of what was know in the art at the time of the instant invention. In the art, it was well recognized that nucleases, specifically RNases, existed in blood plasma or serum, and expected that these enzymes would degrade any extracellular RNA that might otherwise be present in plasma or serum. Such RNases (ribonucleases) were expected to degrade the relatively fragile RNA within seconds. Moreover, RNases were reported to be elevated in the blood of cancer patients. This understanding was not

changed even after disclosure of the Balazs reference. Specific reference to this understanding is included in the following prior art documents, of record in this application:

- Komeda (1995) and Pfleiderer (1995) demonstrated experimentally that free (extracted intracellular) RNA when then mixed with blood within seconds could no longer be detected using PCR amplification.
- Even after the first report by the instant inventor that amplifiable RNA was present in plasma and serum, the finding had been referred to by others as unexpected:
  - Ng et al (2002, pg 1212), "The liability of RNA and the existence of ribonucleases in the plasma make it surprising that circulating RNA should be detectable at all."
  - Tsui et al (2002, pg 1647), "The existence of circulating RNA is a remarkable finding because RNA is more labile than DNA and ribonuclease is known to be present in blood".

The relevance of this understanding is as follows. In keeping with the understanding of the art, the Balazs reference requires the inactivation of such ribonucleases by adding an RNase inhibitor prior to isolating plasma as a condition for detecting RNA from plasma. This requirement is explicitly stated in the reference:

- Balazs (WO), abstract: "under the constant effect of a reliable RNase inhibitor…."

- Balazs (WO), pg 4: "The RNase-handled sample of this same RNA plasma was ineffective."

- Balazs (WO), pg 13: "This task is accomplished by the process as described in Claim 1. The degradation of RNA or its fragments is prevented by the use of an effective and reliable RNase inhibitor that does not induce RNA exudation from the cells, where this inhibitor is used early during specimen collection of the cellular biologic liquid. The fact that the RNase inhibitor does not induce RNA exudation from the cells prior to and during their removal is significant, because this sensitive method can identify even small amounts of contamination." (emphasis added)

- Balazs (WO), pg 14: "The following describes the invention in more detail. The cellular biological liquid (such as blood, exudates, etc.) is mixed with a reliable RNase inhibitor that does not generate RNA cell leakage as early as during specimen collection, and the cells are removed. The total RNA of the resulting acellular biological liquid is mixed with a watery medium with continuous action of the RNase inhibitor …." (emphasis added)

McDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 South Wacker Drive
Chicago, Illinois 60606
(312) 913-0001

- Balazs (WO), pg 16, Example: " 10 ml blood with 20 IE heparin are taken and immediately mixed with a solution of RNase inhibitors such as RNasin.... The blood plasma is separated as quickly as possible." (emphasis added)

In contrast, the methods taught in the instant specification do not require addition of an RNase inhibitor prior to separation of plasma. This is because by adding an RNase inhibitor prior to separation of the cellular and acellular fractions of blood, any method incorporating such RNase inhibitors will stabilize any *intracellular* RNA released from cells during the separation process, and thus provide contaminating intracellular RNA into the plasma. One of ordinary skill would recognize this deficiency in the method disclosed in the Balazs reference, and would understand that as a consequence Balazs does not teach a method that could be used to (unambiguously) detect extracellular RNA in blood plasma. The instant inventor found, surprisingly, that extracellular RNA is sufficiently stable even in the presence of RNases so as to be detectable in human blood plasma or serum without adding RNase inhibitors; indeed, this is evidenced by detection of extracellular RNA species using the methods disclosed in the instant specification. Adding RNases to blood prior to separating the cellular from the acellular portions thereof is unnecessary to stabilize extracellular RNA, but can be expected to stabilize intracellular RNA inadvertently-released from blood cells during separation. The Balazs reference recognizes that intracellular RNA contamination should be avoided, but provides no teachings on how blood separation methods can be modified to prevent it.

Finally, there is no teaching in the Balazs reference for detecting extracellular RNA in serum, which is produced from blood by permitting the blood to clot. Moreover, under the circumstances of clotting it would be expected by the skilled worker that intracellular RNA would be released and stabilized by the introduction (as taught by Balazs) of RNases to whole blood. Thus, the application of the Balazs teachings to serum (not taught by Balazs) would produce a sample likely to be extensively contaminated by intracellularly-derived RNA species.

Applicant respectfully contends that the Balazs reference thus does not teach detection of extracellular RNA of any specifies from blood plasma or serum, and thus does not anticipate the claimed invention.

The claims are non-obvious in view of the cited reference.

Claim 3 stands rejected under 35 U.S.C. 103 over the teachings of the Balazs reference taken in combination with the Revillion reference. Applicant respectfully traverses this ground of rejection.

The deficiencies of the Balazs reference are set forth above. In addition, in the context of non-obviousness the Balazs reference suffers from the following additional deficiencies. The reference does not negate the findings of the art as a whole (such as the Komeda and Pfleiderer reference) that extracellular RNA could not exist in blood plasma or serum under the constant presence of circulating ribonucleases. Instead, the reference suggests that ribonucleases would degrade any RNA found in plasma, as understood by the art, unless an RNase inhibitor was added prior to separating the cellular and acellular portions of blood. In contrast, Applicant's specification teaches that extracellular RNA can be detected in plasma without requiring nuclease inhibitors being added to whole blood prior to separation. This teaching of the instant specification was surprising and unexpected in view of the prior art as a whole, and specifically in view of the Balazs reference, since it was contrary to the notion that extracellular RNA was not detectable in blood plasma or serum due to blood ribonucleases. The understanding of the art, including the Balazs reference, is relevant because it motivated Balazs to introduce RNase inhibitors to blood prior to separating blood cells from plasma, resulting in a plasma-RNAase inhibitor mixture wherein intracellular RNA released from blood cells "broken" during the separation process would have become detectable following the inactivation of naturally occurring RNases.

The teachings of the Revillion reference do not overcome the deficiencies of the Balazs reference. Moreover, the publication date of this reference (1997) is after the claimed priority date of the instant application (1996). Thus, the Revillion reference is not prior art to Applicant's invention. However, Applicant respectfully contends that, even if the teachings of the Balazs reference are taken in combination with the Revillion reference his claimed invention is non-obvious, for the reasons set forth herein.

Applicant thus respectfully requests that the Examiner withdraw this ground of rejection of Claim 3.

While not relevant to Applicant's traversal of the asserted grounds of rejection, and solely to provide a clear record, Applicant notes that the Action asserts that her-2/neu is an epidermal growth factor receptor. As set forth herein, epidermal growth factor receptor and her-2/neu are two distinct receptors, both being classified among the family of tyrosine kinase receptors. The RNA of both, for example would require distinct amplification primers. As further example of the distinction between the two receptors, there are for each specific inhibitor monoclonal antibody therapeutics currently on the market: Herceptin® for her-2/neu and Erbitux® for epidermal growth factor receptor.

CONCLUSIONS

Applicant believes that all grounds of rejection have been overcome by amendment, and request that the pending claims be passed to issue.

If Examiner Lu believes it to be helpful, he is invited to contact the undersigned representative by telephone at (312) 913-0001.

Respectfully submitted,
McDonnell Boehnen Hulbert & Berghoff LLP

Dated: October 29, 2007

By: /Kevin E. Noonan/
Kevin Noonan, Ph.D.
Reg. No. 35,303

McDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 South Wacker Drive
Chicago, Illinois 60606
(312) 913-0001